

# Human Exposure Assessment for Atrazine

By

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## ABSTRACT

This report was prepared as Volume 2 for the Department's risk characterization document for atrazine. The regulatory reason for placing atrazine into the risk assessment process is the conclusion that atrazine, in a 2-year combined chronic and oncogenic feeding study in rats causes mammary tumors. Atrazine is a herbicide used in California as a pre-plant soil treatment to control broadleaf weeds in production agriculture. Metabolism and pharmacokinetic data suggest that after oral dosing, it is rapidly metabolized in animals via oxidative dealkylation of the ethyl and *isopropyl* moieties and conjugation via a mercapturic acid pathway. These metabolic products are eliminated by both fecal and urinary routes. A recent human dermal absorption study yielded a value of 5.6%. There have been a low number of worker illnesses related to exposure to this herbicide. The skin is the primary route of exposure for handlers of atrazine during mixing/loading and applying this herbicide. The Absorbed Daily Dosage for mixer/loader/applicators in production agriculture ranges from 1.8-6.1  $\mu\text{g/kg/day}$ . This range of exposures was derived from a worker exposure study in field corn that employed both passive dosimetry and biological monitoring.

VOLUME 2  
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HUMAN EXPOSURE ASSESSMENT  
ATRAZINE

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## INTRODUCTION

Atrazine, 6-chloro-*N*-ethyl-*N'*-(1-methylethyl)-1,3,5,-triazine-2,4-diamine, is a white crystalline solid (molecular formula C<sub>8</sub>H<sub>14</sub>ClN<sub>5</sub>; CAS # 1912-24-9) that is used as a pre-plant herbicide in production agriculture. Some physical properties of atrazine are listed below:

Melting point (°C)	171-174
Water solubility (ppm)	70
K <sub>ow</sub>	250
Vapor pressure (mm)	3.0 x 10 <sup>-7</sup>
Tomlin, 1994	

## US EPA STATUS

A Reregistration Standard (US EPA, 1983), issued in November 1983, outlined US EPA's regulatory position on products that contain atrazine. With the exception of human exposure issues related to dietary intake of atrazine, there was no requirement for a human exposure assessment for occupational exposures during mixer/loader/applicator work tasks. Recently, a Special Review Notice for atrazine and two other triazine herbicides was published in the Federal Register (US EPA, 1994). This Special Review Notice was prompted by concerns that cancer in humans may result from exposure. This concern is based on the results from animal studies that demonstrated an excess of mammary tumors in female Sprague-Dawley rats for several triazine herbicides.

## USAGE

The use of atrazine for five years is summarized in Table 1. The data in Table 1 indicate that atrazine use has been fairly stable for the 5-year period.

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**Table 1.** Atrazine Use in California for 1993-1998

<u>Year</u>	<u>Use (Pounds)</u>	
	<u>Atrazine</u>	<u>Atrazine, other related</u>
1994	46,497	2,480
1995	36,201	1,939
1996	57,018	3,062
1997	48,568	2,502
1998	54,840	2,943

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ISB (1996,1996a) & DPR (1999, 1999a, 2000)

Atrazine is utilized in California to control broadleaf weeds. In 1998, 54,840 pounds of atrazine were used in the State of California (DPR 2000). Table 2 provides data on application sites for atrazine in 1998 that were greater than 300 lbs. The application sites listed below account for approximately 99% of the use in 1998 (the last year for which data is currently available).

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**Table 2.** Atrazine Use in California 1998

<u>Use</u>	<u>Pounds Applied</u>
Forest trees, Forest lands	15,040
Corn (forage – fodder)	13,779
Sudangrass (forage – fodder, sorghum sudanese)	9,434
Corn (human consumption)	6,797
Bermuda grass (forage – fodder)	6,108
Sorghum/Milo (General)	1,997
Landscape maintenance	975

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DPR, 2000

## FORMULATIONS

Four products are currently registered in the State of California that contain atrazine. Two product formulations are liquids and two are dry flowables. As evidenced by the data in Table 2 most of the products are used for control of weeds in production agriculture.

## LABEL PRECAUTIONS

The Worker Protection Standard labels for atrazine carry the signal word "**CAUTION**" with precautionary statements like those shown below:

**HARMFUL IF SWALLOWED, INHALED OR ABSORBED THROUGH THE SKIN. DO NOT BREATHE DUST OR SPRAY MIST. AVOID CONTACT WITH EYES, SKIN, OR CLOTHING.**

Label requirements for personal protective equipment are as follows:

Applicators

Long-sleeved shirt and long pants  
Water-proof gloves  
Chemical-resistant footwear plus socks

Mixer/Loaders

Long-sleeved shirt and long pants  
Water-proof gloves  
Chemical-resistant footwear plus socks  
Protective eyewear

California regulations require most applicators to wear eye protection.

## **WORKER ILLNESS**

Between the years 1982-1996 there were six illnesses associated with exposure to atrazine or mixtures of atrazine and other pesticides (Orr, 2000). Two cases involved atrazine as the only pesticide with one of these occurring during loading and the other as the result of drift. Two cases occurred during emergency response where multiple pesticides were involved. Finally, two cases occurred during application of atrazine and other pesticides; one was an application using hand-held equipment and the other occurred during a ground application. The eye was the most commonly reported site of injury, with respiratory and systemic symptoms occurring less frequently. Two illnesses resulted from agricultural applications while four resulted from non-agricultural applications. With respect to the illnesses that reported atrazine as the only pesticide, both involved the eye.

## **PLANT RESIDUES**

Products containing this herbicide are soil applied several months before harvest and since it is not applied to the foliage, residues of unmetabolized atrazine on the plant leaf surface (dislodgeable foliar residue) will be below the level of detection. Therefore foliar plant residues as a source of worker exposure will not be considered in this assessment.

## **DERMAL TOXICITY**

Atrazine has an acute dermal toxicity LD<sub>50</sub> in rabbits of 7,500 mg/kg indicating a low order of acute toxicity via this route of administration (Tomlin, 1994). Technical, unformulated atrazine is not a sensitizer in the guinea pig. However, one of the formulations, Aatrex 4L, is a sensitizer in this animal model (Johnson and Sanborn, 1996)

## ANIMAL METABOLISM

Metabolism studies indicate that after an oral dose of  $^{14}\text{C}$ -atrazine, laboratory animals and humans oxidatively remove the *N*-ethyl or *isopropyl* groups. In addition, there is an indication that atrazine is conjugated via the glutathione pathway to eventually form mercapturates that are excreted in the urine. The oxidatively dealkylated degradation products (not mercapturate species) are eliminated either through fecal or urinary routes (Orr, 1987). The ratio of urinary to fecal excretion of radioactivity was about 4:1. While some of the triazine metabolites in rats contained sulfur, metabolism via a glutathione pathway is uncertain because mercapturates were not isolated from the urine for structural confirmation by gas chromatography/mass spectrometry. Apparently, during metabolite isolation the mercapturates did not survive the acidic treatment of the urine extracts. The oxidative transformation products (*N*-dealkylated metabolites) observed in rat urine have been used in biomonitoring studies reported by Ikonen *et al.*, 1988. The metabolism pathways for atrazine in a variety of organisms are comprehensively summarized by Aizawa, 1989. The observation that humans metabolize atrazine via the glutathione pathway was reported in an atrazine exposure study that included biomonitoring. In this study the mercapturate of atrazine was identified as the primary immuno-reactive urinary metabolite (Lucas *et al.*, 1993).

## DERMAL ABSORPTION

### *In Vivo* Dermal Absorption: Human Skin

The registrant submitted an interim report of an *in vivo* dermal absorption study in human volunteers (Hui, *et al.*, 1995). T. Thongsinthusak has reviewed the study. The following paragraphs were taken from the memorandum sent to P. Anderson as a part of the ongoing registration for atrazine (Thongsinthusak, 1997).

The Surge Laboratory of the University of California, San Francisco conducted an *in vivo* dermal absorption study of atrazine in human volunteers. The study was completed on October 25, 1995. As indicated in the submitted reports, this study was not conducted in compliance with the U.S. EPA Good Laboratory Practice Standards (40 CFR, part 160). However, the study director provided a written statement to indicate that this study was conducted under Good Scientific Practices and in general compliance with the spirit of Good Laboratory Practice Standards. The following provides a brief description and results of the study.

*Human volunteers* - Twelve healthy male volunteers, aged from 43 to 74 years, were recruited from the University of California, San Francisco, and the surrounding San Francisco Bay Area community. Six volunteers were used for group A (low dose) and six volunteers were used for group B (high dose). However, two volunteers were dismissed from the low dose group due to improper collection of urine samples on the first day.

*Dose preparation and application* - Volunteers in group A received a dose of  $6.7 \mu\text{g}/\text{cm}^2$  and those in group B received  $79 \mu\text{g}/\text{cm}^2$ . The dosing solution was

prepared by mixing the appropriate amount of  $^{14}\text{C}$ -atrazine (98.4 % pure) and 4L formulation in deionized water. The prepared dosing solution was applied to 25  $\text{cm}^2$  (2.0 cm x 12.5 cm) of the left ventral forearm of each volunteer. The application was accomplished by using a 0.1-mL Teflon-coated syringe. After topical application, the dosed area was allowed to air dry. Then, a non-occlusive plastic cover was secured over the dosed area and kept in place for 24 hrs. The cover was shaped as a half round cylinder with three open holes on the top which allowed air circulation from both sides and top. The volunteers were instructed not to touch or wash the treated area for 24 hrs.

*Sample collection and analysis* - At 24 hrs after dosing, the plastic cover was removed and the treated skin was washed alternately with the Ivory liquid soap solution (50%, v/v) and deionized water for two cycles. The fifth washing was done with deionized water. At 168 hours after dosing, the dosed skin was stripped 10 times with cellophane tape. The volunteers were instructed to collect urine and feces samples one hour before dosing and after dosing.. The samples were kept in a cooler containing dry ice and ice packs during each collection period. Samples collected for analysis were urine, feces, skin washes, tape strips, and non-occlusive covers. All samples were prepared and radioactivity measurements were conducted using a model 1500 Packard Liquid Scintillation Counter.

*Results and discussion* - The (arithmetic) mean dose recovered in urine was 5.03% for the low dose and 1.11% for the high dose. Excretion of the dose in feces was much lower than that in urine. The majority of the administered dose was found in the skin wash sample with a mean of 95.4% for the low dose and 91.0% for the high dose. The mass balance for both doses is very good: 101.2% for the low dose and 92.3% for the high dose.

As indicated in the same submitted report, an IV administration of atrazine was conducted in rhesus monkeys (Hui *et al*, 1995). At 168 hours after a single IV dose,  $84.84 \pm 5.60\%$  of the administered dose was recovered in urine and  $11.73\% \pm 1.90\%$  was recovered in feces; the overall recovery of the dose was  $98.92 \pm 5.87\%$ . The studies in monkeys and in human volunteers revealed that atrazine is not likely to accumulate in tissues or blood after 168 hours following topical or IV administration. Based on these observations, the dermal absorption rate for atrazine is simply the total dose excreted in urine and feces. The estimated dermal absorption values were  $5.6 \pm 3.1\%$  for the low dose and  $1.2 \pm 1.0\%$  for the high dose.

*Recommendations* - The dermal absorption study of atrazine in human volunteers is appropriate for use in the determination of the dermal absorption rate. The low dose of  $6.7 \mu\text{g}/\text{cm}^2$  is representative of exposure agricultural workers would experience. Dermal absorption of 5.6% will be used in determining absorbed dosages of atrazine in humans. The dermal absorption of 1.2% for the high dose ( $79 \mu\text{g}/\text{cm}^2$ ) may be appropriate for use in determining absorbed dosages of atrazine in formulation workers or to other workers who may experience a high

level of exposure. These recommendations assume the data in the interim report will be the same as those in the final report.

Previous versions of this exposure assessment reviewed and summarized several laboratory dermal absorption studies. Because of the foregoing human *in vivo* dermal absorption study, a dermal absorption value from these studies is not appropriate for the assessment of exposure. The list of these studies is contained in the appendix.

## **WORKER EXPOSURE**

The registrant submitted a contemporary study that evaluated handler exposure to atrazine during treatment prior to planting field corn. Atrazine handlers were monitored during a pre-plant application for control of weeds in field corn grown in the Midwest (Selman and Rosenheck, 1996; Honeycutt, et al., 1996; Selman, 1996). Thirty-six separate mixing/loading/truck tending and applying replicates were monitored. Five of the exposure replicates combined mixing/loading/truck tending with application. Table 4 lists the distribution of replicates for the various work scenarios *i.e.*, mixing/loading/applying. Some monitored workers had previous exposure to atrazine as they were in the middle of their treatment season; others had no previous exposure. In most replicates, two layers of dosimetry media were used, an outer (long-sleeved shirt, pants) and inner long-sleeved shirt and briefs. The latter dosimeters collected the residues that would normally reach the skin. In some of the replicates, because of cold weather, an additional sweatshirt was worn. The sweatshirt then functioned as the outer dosimeter and the long sleeve shirt worn underneath was then inner dosimeter. When the additional layer was worn, the titers of urinary metabolites were about 5-6 fold less than when the additional layer was not worn. Hand exposure was estimated with hand washes. While mixing/loading, the workers wore chemical resistant nitrile gloves. Head and neck exposure was estimated from patches on the hat of the workers. Personal air pumps and sampling media were used to assess inhalation exposure. Residues on the "briefs" were extrapolated to provide an estimate of exposure for the lower body.

In addition, urinary monitoring was conducted. If the workers were in the middle of their application season, interpretation of the urinary metabolite data requires an assumption. Because the workers may or may not have previous exposure to atrazine, the most appropriate use of the urinary metabolite information is to assume that the metabolite concentrations are at steady state. Chloro triazine urinary metabolites were used to assess exposure. The basis for these metabolites as indicators of exposure comes from a study where volunteers, dosed orally with atrazine, excreted them in the urine (Cheung, 1990).

The exposure data from both passive dosimetry and urinary monitoring studies are reported in Table 3 and were used to calculate a central tendency for chronic toxicology endpoints (geometric mean) and an upper exposure value (95<sup>th</sup> percentile) for acute toxicology endpoints. Examination of the data from these three studies described above lead to the calculation of geometric mean for all the data because no apparent

relationship existed between exposure and pounds handled. The absence of a relationship between pounds handled and exposure maybe not be unexpected because of the range of pounds handled (<100 - 2,500 lbs) likely required a variety of handling equipment. It is implausible that a single person would be able to load 2500 pounds from atrazine in bags or small containers. Rather this amount of atrazine was pumped in to the application equipment from a nurse tank. Since no relationship exists between pounds handled and exposure, no adjustment of the exposure is made for the amount applied for treatment of corn (~150 pounds ai/day) in the California. The amount handled lies in the range applied during the exposure studies conducted in the Midwest in field corn. In the calculations of absorbed daily dosages (ADD), the human dermal absorption value of 5.6% was used. The calculations used body weights of study participants.

**Table 3.** Absorbed Daily Doses (ADD) for Preplant Treatment of Field Corn With Atrazine from Passive Dosimetry and Urinary Monitoring

Passive Dosimetry						Urinary Monitoring		
		Exposure (µg/person)		ADD <sup>d/</sup> (µg/kg/day)		Exposure (µg/person)	ADD (µg/kg/day)	
		Dermal	Inhalation	(dermal +inhalation)				
Activity	n	GM <sup>c/</sup>	GM	GM	95 <sup>th</sup> Percentile <sup>e/</sup>	GM	GM	95 <sup>th</sup> Percentile
Apply	14	4134	0.35	3.17	76.17	175	2.26	10.18
M/L/T <sup>a/</sup>	16	4477	1.30	2.90	90.94	193	2.13	12.80
M/L/T/A <sup>b/</sup>	6	2813	0.25	1.77	8.59	412	4.57	27.79

a/ M/L/T-Mixing, loading, and tending  
b/ Combined monitoring: mixing (M), loading (L), tending (T) and applying, (A)  
c/ Geometric Mean  
d/ Absorbed Daily Dosage: body weights as reported in the study, dermal absorption 5.6%  
e/ 95<sup>th</sup> percentile = GM x GSD<sup>1.645</sup>

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Several aspects of these data deserve comment. The ADDs from the passive dosimetry and urinary monitoring differ by less than three-fold, despite no dermal estimate for leg exposure. This small difference suggests that the 5.6% value for dermal absorption is valid and that the urinary metabolites are at steady state.

Since this exposure study used contemporary dosimetry methodology (whole body dosimetry, hand washes instead of cotton gloves for the hand exposure and biological monitoring) and was conducted under Good Laboratory Practices, these exposure estimates should be used to derive risks associated with handling atrazine.

The ADDs in Table 3 for combined mixing/loading and applying are similar to ADDs calculated by Lunchik and Selman (1998) using the generic Pesticide Handlers Exposure Database (PHED) (Versar, 1995), for the exposure estimates. Lunchik and Selman (1998) calculated ADD values from several versions of PHED that ranged from 1.5-6.4 µg/kg/day for ground boom applications with open or closed loading and open or

closed cabs for application. These calculations assumed 1.5 lbs/acre (calculated from California Pesticide Use Report data), 100 acres per day (Haskell, 1998) and 5.6% dermal penetration from an *in vivo* human study. These PHED-based exposure estimates antedate the human exposure study by the registrant that combined passive dosimetry with biological monitoring. The similarity of the PHED-derived absorbed daily doses to those from the combined dermal dosimetry and biological monitoring indicate in this instance that PHED was a good predictor of absorbed dose.

Up to this point, estimates for daily exposures have been reported. Since there are subchronic and chronic toxicological endpoints that need consideration, annual and lifetime daily absorbed dosages are estimated for comparison with the animal toxicology data. These values are influenced by whether the mixer/loader/applicator is a farmer-grower or a commercial applicator and whether the tasks (mixing/loading/applying) were monitored separately or combined.

For the purposes of estimating risks associated with handling atrazine, an ADD range of 1.8-6.1 (3.2+2.9)  $\mu\text{g/kg/day}$  should be used for comparison for toxicology endpoints that are either subchronic or chronic. The amortized exposure values are collected in Table 4.

**Table 4.** ADD, AADD and LADD Values for Ground Application of Atrazine for Grower and Commercial Applicators - Field Corn Application

<u>Exposure Scenario</u>	<u>Exposure (<math>\mu\text{g/kg-bw/day}</math>)</u>					
	<u>ADD<sup>a/</sup></u>		<u>AADD<sup>d/</sup></u>		<u>LADD<sup>e/</sup></u>	
Load/Apply (separate monitor)						
Farmer-Grower	6.07 <sup>b/</sup>	(4.39) <sup>b,c/</sup>	0.05	(0.036)	0.027	(0.019)
Commercial	6.07 <sup>b/</sup>	(4.39) <sup>b/</sup>	0.25	(0.18)	0.13	(0.096)
Load/Apply (combined monitor)						
Farmer-Grower	1.77	(4.57)	0.015	(0.038)	0.008	(0.02)
Commercial	1.77	(4.57)	0.073	(0.19)	0.039	(0.10)
a/ From Table 3 b/ This value is the sum of the "Apply" and "M/L/T" exposures that were measured separately c/ Exposure values in parentheses were derived from urinary monitoring d/ Annual Average Daily Dosage: Annual Exposure Days – Farmer-Grower = 3; Commercial Applicator = 15 (Haskell, 1998); AADD = ADD (3 or 15 days)/365 days e/ Lifetime Average Daily Dosage: Lifetime Exposure = 40 Years; Life Expectancy = 75 years, LADD = AADD x 40 years/75 years						

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## Exposure Appraisal

### Chronic Exposure

Exposure estimates for mixer/loader/applicators were derived from a contemporary study using whole body dosimetry. The human *in vivo* dermal absorption study obviates the use of dermal absorption values from laboratory animals. The ADD values from an exposure study of workers treating corn with atrazine ranged from 1.8-6.1 µg/kg/day. This range of ADD values should be the starting point for the estimation of chronic risks associated with handling atrazine.

### Acute Exposure

It maybe necessary to estimate acute risks associated with handling atrazine. For acute risk estimation, historically DPR has utilized a variety of upper bound values such as the 95<sup>th</sup> percentile, the mean + 2 standard deviations (97.5 percentile), or even the 99<sup>th</sup> percentile exposure. The most appropriate exposure values for estimation of possible acute risks from handling atrazine should be taken from Table 3. In this table, 95<sup>th</sup> percentile values for the ADD were calculated from the geometric mean and geometric standard deviation. Further, for ADD values derived from urinary monitoring, the ratios of the 95<sup>th</sup> percentile to the geometric mean were less than 6.

Many other studies were reviewed during the evaluation of atrazine exposure. A discussion of those studies and the reasoning for not using that data are discussed in the appendix to this document.

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## Appendix

### **Studies reviewed but not used in the exposure assessment document**

#### Overview

The exposure assessment for atrazine was first completed in 1989 and then revised in 1991 and 2000. Subsequently, new data have been submitted by the registrant that has made some of the information used in earlier revisions obsolete and therefore the use in the current exposure assessment is inappropriate. The two main areas where new information exists are in the areas of dermal absorption and worker exposure.

#### Dermal Absorption

Several dermal absorption studies listed below have been deleted from the exposure assessment document. The earlier dermal studies either involved laboratory animals or *in vitro* studies. Since the last revision of the exposure assessment, a human *in vivo* dermal study has been submitted (Hui *et al.*, 1995). Therefore the data from the studies listed below have not been used for the exposure estimate.

Williams, S.C. and Marco, G.J. (1983) Excretion rate study from rats dermally dosed with <sup>14</sup>C-atrazine. CIBA-GEIGY Report No. ABR 83063. DPR Reg. Doc. No. 220-113.

Murphy, T. and Simoneaux, B. (1987) Dermal absorption of <sup>14</sup>C-atrazine in the rat. CIBA-GEIGY Report No. ABR 87098. DPR Reg. Doc. No. 220-113.

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#### Exposure

In previous drafts of the atrazine exposure assessment, several worker exposure scenarios were characterized. Since that time, some of the uses, such as industrial weed control and right-of-way applications, have been removed from the label. Only production agriculture applications are allowed by the current version of the label. Therefore, it is not appropriate to characterize the exposure for these other handling scenarios. While previous atrazine exposure assessments contained an exposure

assessment for production agriculture Ballantine and Hensley, 1981, study did not use contemporary dosimetry techniques, did not utilize urinary monitoring data that was based on pharmacokinetic information in humans and did not have the requisite number of subjects in the study. Therefore the studies of Honeycutt, *et al.*, 1996. Selman, *et al.*, (1996) and Selman, F.B. (1996) have been used to estimate worker exposure for atrazine handlers during application to field corn. These three studies utilized contemporary dermal dosimetry methodology and biological monitoring that was based on information on pharmacokinetics in humans. The following studies that estimated human exposure during handling have been deleted from this exposure assessment.

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